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ATTORNEY DOCKET NO. 10030355-1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventor(s): Paul K. Wolber et al.

Serial No.: 10/699,281 **Examiner:** Crow, Robert T.

Filing Date: October 30, 2003 **Group Art Unit:** 1634

Title: NUCLEIC ACID ARRAYS COMPRISING DEPURINATION PROBE FEATURES AND METHODS FOR USING THE SAME

COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria VA 22313-1450

TRANSMITTAL OF APPEAL BRIEF

Sir:

Transmitted herewith is the Appeal Brief in this application with respect to the Notice of Appeal filed on April 20, 2007 .

The fee for filing this Appeal Brief is (37 CFR 1.17(c)) **$500.00**.

(complete (a) or (b) as applicable)

The proceedings herein are for a patent application and the provisions of 37 CFR 1.136(a) apply.

☐ (a) Applicant petitions for an extension of time under 37 CFR 1.136 (fees: 37 CFR 1.17(a)(1)-(5)) for the total number of months checked below:

☐	one month	$ 120.00
☐	two months	$ 450.00
☐	three months	$1020.00
☐	four months	$1590.00

☐ The extension fee has already been filled in this application.

☒ (b) Applicant believes that no extension of term is required. However, this conditional petition is being made to provide for the possibility that applicant has inadvertently overlooked the need for a petition and fee for extension of time.

Please charge to Deposit Account **50-1078** the sum of $500.00 . At any time during the pendency of this application, please charge any fees required or credit any overpayment to Deposit Account **50-1078** pursuant to 37 CFR 1.25.

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Respectfully submitted,

Paul K. Wolber et al.

By [signature]

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Rev 06/05 (AplBrief)

33 TOTAL PAGES

VIA EXPRESS MAIL EV 687639405 US

APPELLANTS' BRIEF Address to: Mail Stop Appeal Brief-Patents Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450	Application Number	10/699,281
	Confirmation Number	3574
	Attorney Docket No.	10030355-1
	Filing Date	October 30, 2003
	First Named Inventor	WOLBER, PAUL K.
	Examiner	CROW, ROBERT
	Group Art	1634
	Title: NUCLEIC ACID ARRAYS COMPRISING DEPURINATION PROBE FEATURES AND METHODS FOR USING THE SAME	

Sir:

This Brief is filed in support of Appellants' appeal from the Examiner's Rejection dated December 12, 2006. No claims have been allowed. Claims 1-13 and 21-25 are pending and appealed herein. A Notice of Appeal was filed on April 20, 2007.

The Board of Appeals and Interferences has jurisdiction over this appeal pursuant to 35 U.S.C. §134.

The Commissioner is hereby authorized to charge deposit account number 50-0815, reference no. 10030355-1 to cover the fee required under 37 C.F.R. §1.17(b) for filing Appellants' brief. In the unlikely event that the fee transmittal or other papers are separated from this document and/or other fees or relief are required, Appellants petition for such relief, including extensions of time, and authorize the Commissioner to charge any fees under 37 C.F.R. §§ 1.16, 1.17 and 1.21 which may be required by this paper, or to credit any overpayment, to deposit account number 50-0815, reference no. 10030355-1.

TABLE OF CONTENTS

REAL PARTY IN INTEREST

The inventors named on this patent application assigned their entire rights to the invention to Agilent Technologies, Inc.

RELATED APPEALS AND INTERFERENCES

There are currently no other appeals or interferences known to Appellants, the undersigned Appellants' representative, or the assignee to whom the inventors assigned their rights in the instant case, which would directly affect or be directly affected by, or have a bearing on the Board's decision in the instant appeal.

STATUS OF CLAIMS

The present application was filed on October 30, 2003 with Claims 1-28. During the course of prosecution, Claims 14-20 and 26-28 were withdrawn. Accordingly, Claims 1-13 and 21-25 are pending in the present application, all of which stand rejected. All of the rejected claims are appealed herein.

STATUS OF AMENDMENTS

Amendments to Claims 1 and 21 were filed subsequent to issuance of the Final Rejection. In the Advisory Action, the Examiner indicated that these amendments would be entered for purposes of appeal.

SUMMARY OF CLAIMED SUBJECT MATTER

The claimed invention is drawn to a method of detecting the presence of a nucleic acid analyte in a sample.

Below is a description of each appealed claim and where support for each can be found in the specification.

Claim 1 claims a method of detecting the presence of depurination reaction products on a surface of an in situ produced nucleic acid array, the method including:

> (a) contacting an in situ produced nucleic acid array that includes at least one depurination probe feature having a depurination probe with a sample including a target nucleic acid that specifically binds to the

depurination probe; and

(b) detecting the amount of resultant binding complexes of the depurination probe and the target nucleic acid in the depurination probe feature to determine the presence of depurination reaction products on the surface.

(see specification at page 5, lines 18-30).

Claim 2 claims the method according to Claim 1, in which the method is a method of determining the amount of depurination reaction products on the surface (see specification at page 23, lines 28-29).

Claim 3 claims the method according to Claim 2, in which the amount is a relative amount (see specification at page 23, lines 19-22).

Claim 4 claims the method according to Claim 1, in which the target nucleic acid is labeled and the detecting including detecting a signal from the depurination probe feature (see specification at page 23, lines 15-27).

Claim 5 claims the method according to Claim 4, in which the label is fluorescent and the signal is a fluorescent signal (see specification at page 27, lines 7-11).

Claim 6 claims the method according to Claim 5, in which the fluorescent signal has an intensity that is inversely proportional to the amount of depurination reaction products in the depurination probe feature (see specification at page 23, line 28 through page 24, line 10 and in original claim 6).

Claim 7 claims the method according to Claim 1, in which the array includes two or more different depurination probe features each corresponding to a distinct depurination probe (see specification at page 15, lines 7-10).

Claim 8 claims the method according to Claim 7, in which the array includes at least one early depurination probe feature and at least one late depurination probe feature (see specification at page 17, lines 18-25).

Claim 9 claims the method according to Claim 1, in which the array includes two or more identical depurination probe features whose synthesis was started at different times (see specification at page 18, lines 16-27).

Claim 10 claims the method according to Claim 1, in which the depurination probe has a known deblock dose (see specification throughout pages 19-22).

Claim 11 claims the method according to Claim 1, in which the method further includes evaluating the level of depurination that occurred during in situ fabrication of

the array (see specification at page 14, lines 29-31).

Claim 12 claims the method according to Claim 11, in which the method is a method of evaluating the quality of an in situ nucleic acid array synthesis fabrication protocol (see specification at page 25, lines 6-14).

Claim 13 claims the method according to Claim 12, in which the method is employed to evaluate the quality of a plurality of nucleic acid arrays fabricated according to the protocol (see specification at page 25, lines 21-34).

Claim 21 claims a method of detecting the presence of a nucleic acid analyte in a sample, the method including:

(a) contacting a nucleic acid array including a set of two or more nucleic acid depurination features each having a depurination probe and a nucleic acid ligand that specifically binds to the nucleic acid analyte with a sample suspected of including the analyte under conditions sufficient for binding of the analyte to the nucleic acid ligand on the array to occur; and

(b) detecting the presence of binding complexes of the nucleic acid ligand and the analyte on the surface of the array to detect the presence of the nucleic acid analyte in the sample (see specification at page 26, line 30 through page 27, line 29).

Claim 22 claims the method according to Claim 21, in which the sample includes a collection of labeled target nucleic acids that specifically bind to the nucleic acid depurination features (see specification at page 27, lines 13-22).

Claim 23 claims a method including transmitting a result from a reading of an array according to the method of Claim 21 from a first location to a second location (see specification at page 27, line 30 through page 28, line 13).

Claim 24 claims the method according to Claim 23, in which the second location is a remote location (see specification at page 27, lines 30-32).

Claim 25 claims a method including receiving a transmitted result of a reading of an array obtained according to the method Claim 21 (see specification at page 29, lines 1-3).

GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

I. Claims 21-25 stand rejected under 35 U.S.C. § 102(b) as being anticipated by McGall (US Patent No. 5,843,655).

II. Claims 1-13 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over McGall in view of Weng *et al.* (US Patent No. 6,691,042).

ARGUMENT

In the arguments set forth below, the Appellants will argue the rejected claims in Groups as follows:

Group I: Claims 1-7 and 10-12, drawn to a method of detecting the presence of depurination reaction products on a surface of an in situ produced nucleic acid array, the method including contacting an in situ produced nucleic acid array that includes at least one depurination probe feature having a depurination probe with a sample including a target nucleic acid that specifically binds to the depurination probe and detecting the amount of resultant binding complexes of the depurination probe and the target nucleic acid in the depurination probe feature to determine the presence of depurination reaction products on the surface;

Group II: Claim 8, drawn to the method according to Claim 7, in which the array includes at least one early depurination probe feature and at least one late depurination probe feature;

Group III: Claim 9, drawn to the method according to Claim 1, in which the array includes two or more identical depurination probe features whose synthesis was started at different times;

Group IV: Claim 13, drawn to the method according to Claim 12, in which the method is employed to evaluate the quality of a plurality of nucleic acid arrays fabricated according to the protocol;

Group V: Claims 21 and 23-25, drawn to a method of detecting the presence of a nucleic acid analyte in a sample, the method including contacting a nucleic acid array including a set of two or more nucleic acid depurination features each having a depurination probe and a nucleic acid ligand that specifically binds to the nucleic acid analyte with a sample suspected of including the analyte under conditions sufficient for binding of the analyte to the nucleic acid ligand on the array to occur and detecting the presence of binding complexes of the nucleic acid ligand and the analyte on the surface of the array to detect the presence of the nucleic acid analyte in the sample; and

Group VI: Claim 22, drawn to the method according to Claim 21, in which the sample includes a collection of labeled target nucleic acids that specifically bind to the nucleic acid depurination features.

I. Claims 21-25 are not anticipated under 35 U.S.C. § 102(b) by McGall (US Patent No. 5,843,655).

Group V: Claims 21, 23-25

As described above, independent Claim 21 is drawn to a method of detecting the presence of a nucleic acid analyte in a sample, the method including contacting a nucleic acid array including a set of two or more nucleic acid depurination features each having a depurination probe and a nucleic acid ligand that specifically binds to

the nucleic acid analyte with a sample suspected of including the analyte under conditions sufficient for binding of the analyte to the nucleic acid ligand on the array to occur; and detecting the presence of binding complexes of the nucleic acid ligand and the analyte on the surface of the array to detect the presence of the nucleic acid analyte in the sample.

A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. *Verdegaal Bros. v. Union Oil of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987).

The Examiner has rejected the claims of this Group as being anticipated by McGall. In making this rejection, the Examiner asserts that McGall teaches each and every element of the claims.

For the reasons detailed below, the Appellants submit that McGall fails to anticipate the claimed invention. Specifically, the Appellants submit that McGall fails to teach, either expressly or inherently, contacting a nucleic acid array including features each having a depurination probe and a nucleic acid ligand that specifically binds to a nucleic acid analyte with a sample suspected of including the analyte under conditions sufficient for binding of the analyte to the nucleic acid ligand on the array to occur, detecting of a resultant binding complex and detection of the presence of an analyte in a sample, as is claimed.

In the Final Rejection of December 22, 2006, the Examiner asserted that McGall teaches these elements and anticipates the claimed invention. In sustaining this rejection the Examiner points to Figure 8 of McGall and asserts that "oligonucleotides marked with a 'D' are depurination probes" and that the array containing these depurination probes is treated with a sample suspected of containing a nucleic acid analyte. The Appellants respectfully disagree and contend that the Examiner has mischaracterized the cited art.

The Appellants replied in the communication of February 6, 2007 that McGall is directed to determining the extent of depurination of oligonucleotides on a substrate that results from a given testing condition, which method includes the use of a substrate containing oligonucleotide linkers having an active site for coupling of nucleotides. The linkers are resistant to cleavage under alkaline conditions. Labels are attached to the linkers. The substrate is then exposed to a test condition. The test condition is one that is to be evaluated for its capacity to cause depurination, and therefore loss from the substrate, of the linkers. Following exposure to the test conditions, the substrate is exposed to alkaline conditions. The purpose of exposing the substrate to alkaline conditions is retention of any linkers which were not cleaved under the test condition, since depurinated oligonucleotides are prone to backbone cleavage when exposed to alkaline conditions. Any depurinated oligonucleotides produced will be cleaved from the substrate and the labeled probes which remain can be quantitated so as to determine the extent of the depurination caused by the test conditions (please consult McGall, column 11, lines 20 to 51).

As such, to the extent that McGall discloses determining the amount of depurination, it is with respect to subjecting the substrate to a test condition, and then determining the extent of any resultant depurination by quantitating any oligonucleotides which remain attached to the substrate.

In contradistinction, the instant claims specifically recite contacting a nucleic acid array including a set of two or more nucleic acid depurination features each having a depurination probe and a nucleic acid ligand that specifically binds to the nucleic acid analyte with a sample suspected of including the analyte under conditions sufficient for binding of the analyte to the nucleic acid ligand on the array to occur.

At no point in the process of McGall is the substrate contacted with a sample suspected of including an analyte; the objects of analysis of McGall are synthesized *in situ* on the substrate prior to the assay. Hence, there is no binding of an analyte to any of the probes, there is no detecting of a binding complex and there is no

detection of the presence of an analyte in a sample taught by McGall. Rather, the synthesized probes are merely labeled and subjected to a test condition, wherein one or more of the labeled probes may be cleaved from the array due to a depurination event. The sole detection step is the detection of probes remaining on the substrate subsequent to exposure to the test condition.

Moreover, the Examiner cites column 13, lines 33-52 of McGall multiple times as allegedly teaching treatment of an array with a sample suspected of containing an analyte under conditions sufficient for binding, detecting the presence of nucleic acid analytes in the sample, and that the sample includes a collection of labeled target nucleic acids that specifically bind to the nucleic acid depurination features (Final Rejection, page 3).

The Appellants submit that this cited passage, also, is incorrectly interpreted by the Examiner. In addition to the Section V "Rates of Depurination" technique from which the other passages cited by the Examiner are taken (column 9, line 22), the disclosure of McGall teaches several other techniques (please consult McGall, column 6, line 12; column 6, line 27; column 8, line 50; column 10, line 35).

Following the description of the different techniques, McGall then provides a general discussion of signal detection and interpretation (please consult McGall, column 11, line 52), in which is discussed a laundry list of issues relating to the use of arrays with CCD image detection devices, computers and data analysis. It is this section of the disclosure which the Examiner cites as describing the claimed elements.

However, as is plain to one of skill in the art, McGall establishes no relationship between the "target nucleic acids" of column 13 and any molecules mentioned in the "Rates of Depurination" technique which would communicate the presence of the claimed elements. Specifically, by way of example, McGall nowhere teaches "hybridization" of the *in situ*-synthesized probes to "target nucleic acids" which would have an "on- or off-rate," and nowhere teaches that the labeled *in situ*-

synthesized probes, once cleaved from the substrate by a test condition, would or could reanneal at any rate such that an "equilibrium" could be measured. The citation is made out of context and, as such, constitutes quintessential cherry picking of phrases from a reference in order to cobble together the Appellants' invention.

Accordingly, the cited passages and figure provide no description of the claimed elements and, indeed, make clear the distinctions between McGall and the claimed method, as discussed above.

In maintaining the rejection, the Examiner asserts in the Advisory Action of March 7, 2007 that the amended claims would be rejected under 35 USC 103(a) for the reasons set forth in the rejection of claims 1-13 under 35 USC 103(a) as indicated in the Final Rejection and as outlined in the Advisory Action.

The Appellants firstly note that, in the rejection of claims 1-13 under 35 USC 103(a) in the Final Rejection of December 22, 2006, the Examiner acknowledges that "McGall does not explicitly show hybridization as a test condition for determining depurination" (page 5), as is claimed.

The Appellants secondly note that, in the Advisory Action of March 7, 2007, the Examiner acknowledges that "the specific embodiment of hybridization of a nucleic acid, which is a target, to the array followed by cleavage," as is claimed, "is not explicitly taught by McGall" (page 2).

Accordingly, the Appellants submit that, since the Examiner provides no new reasoning or argument which would support an obviousness rejection over McGall absent a secondary reference, Claims 21 and 23-25 are not anticipated under 35 U.S.C. § 102(b) by McGall.

Group VI: Claim 22

As described above, independent claim 21 is drawn to a method of detecting

the presence of a nucleic acid analyte in a sample, the method including contacting a nucleic acid array including a set of two or more nucleic acid depurination features each having a depurination probe and a nucleic acid ligand that specifically binds to the nucleic acid analyte with a sample suspected of including the analyte under conditions sufficient for binding of the analyte to the nucleic acid ligand on the array to occur; and detecting the presence of binding complexes of the nucleic acid ligand and the analyte on the surface of the array to detect the presence of the nucleic acid analyte in the sample.

Claim 22, which depends from Claim 21, is drawn to the method according to Claim 21, in which the sample includes a collection of labeled target nucleic acids that specifically bind to the nucleic acid depurination features.

The Examiner has rejected the claims of this Group as being anticipated by McGall. In making this rejection, the Examiner asserts that McGall teaches each and every element of the claims.

For the reasons detailed above, the Appellants submit that McGall fails to teach, either expressly or inherently, contacting a nucleic acid array including features each having a depurination probe and a nucleic acid ligand that specifically binds to a nucleic acid analyte with a sample suspected of including the analyte under conditions sufficient for binding of the analyte to the nucleic acid ligand on the array to occur, detecting of a resultant binding complex and detection of the presence of an analyte in a sample, as is claimed.

With regard to the rejection of the claims in this Group, the Appellants submit that McGall further fails to teach a sample including a collection of labeled target nucleic acids that specifically bind to the nucleic acid depurination features.

Specifically, since McGall fails to teach hybridization, McGall further fails to teach a collection of labeled target nucleic acids that specifically bind to the nucleic acid depurination features. Accordingly, Claim 22 is not anticipated by McGall.

With regard to Claim 22, the Examiner cites column 13, lines 33-52 of McGall multiple times as allegedly teaching treatment of an array with a sample suspected of containing an analyte under conditions sufficient for binding, detecting the presence of nucleic acid analytes in the sample, and that the sample includes a collection of labeled target nucleic acids that specifically bind to the nucleic acid depurination features (Final Rejection, page 3).

As discussed in detail above, the Appellants submit that this cited passage is incorrectly interpreted by the Examiner, since it is plain to the ordinarily skilled artisan that McGall establishes no relationship between the "target nucleic acids" of column 13 and any molecules mentioned in the "Rates of Depurination" technique which would communicate the presence of the claimed elements. Specifically, by way of example, McGall nowhere teaches "hybridization" of the *in situ*-synthesized probes to "target nucleic acids" which would have an "on- or off-rate," and nowhere teaches that the labeled *in situ*-synthesized probes, once cleaved from the substrate by a test condition, would or could reanneal at any rate such that an "equilibrium" could be measured. The citation is made out of context and, as such, constitutes quintessential cherry picking of phrases from a reference in order to cobble together the Appellants' invention.

In view of the discussion above, the Appellants submit that McGall (US Patent No. 5,843,655) fails to anticipate the claims of Groups V and VI, and respectfully request reversal of the rejection.

II. Claims 1-13 are not obvious under 35 U.S.C. § 103(a) over McGall (US Patent No. 5,843,655) in view of Weng *et al.* (US Patent No. 6,691,042).

It is respectfully submitted that the Examiner's *prima facie* case of obviousness is deficient because the combined teachings of McGall and Weng *et al.* (hereinafter "Weng") fail to teach or suggest each and every element of the claimed

invention.

Group I: Claims 1-7

As noted above, the claims of this Group are drawn to a method of detecting the presence of depurination reaction products on a surface of an in situ produced nucleic acid array, the method including contacting an in situ produced nucleic acid array that includes at least one depurination probe feature having a depurination probe with a sample including a target nucleic acid that specifically binds to the depurination probe and detecting the amount of resultant binding complexes of the depurination probe and the target nucleic acid in the depurination probe feature to determine the presence of depurination reaction products on the surface.

The Examiner acknowledges that McGall is deficient in that it fails to teach or suggest the use of a hybridization condition as a test condition for determining depurination (Final Rejection, page 5; Advisory Action, page 2). The Examiner, therefore, relies upon Weng to remedy the deficiencies of McGall. The Office asserts that it would have been obvious to modify the depurination test conditions as taught by McGall with the hybridization conditions disclosed in Weng.

To establish a *prima facie* case of obviousness, the prior art reference, or references when combined, must teach or suggest all the claim limitations. *In re Royka*, 180 USPQ 580 (CCPA 1974).

The Appellants submit that a *prima facie* case of obviousness has not been established because the combination of references fails to teach or suggest all the elements of the rejected claims.

McGall is directed to determining the extent of depurination of oligonucleotides on a substrate that results from a given testing condition, which method includes the use of a substrate containing oligonucleotide linkers having an active site for coupling of nucleotides. The linkers are resistant to cleavage under alkaline conditions. Labels are attached to the linkers. The substrate is then

exposed to a test condition. The test condition is one that is to be evaluated for its capacity to cause depurination, and therefore loss from the substrate, of the linkers. Following exposure to the test conditions, the substrate is exposed to alkaline conditions. The purpose of exposing the substrate to alkaline conditions is retention of any linkers which were not cleaved under the test condition, since depurinated oligonucleotides are prone to backbone cleavage when exposed to alkaline conditions. Any depurinated oligonucleotides produced will be cleaved from the substrate and the labeled probes which remain can be quantitated so as to determine the extent of the depurination caused by the test conditions (please consult McGall, column 11, lines 20 to 51). Specifically, in McGall, the "probe" has no corresponding "target".

As such, to the extent that McGall discloses determining the amount of depurination, it is with respect to subjecting the substrate to a test condition, and then determining the extent of any resultant depurination by quantitating any oligonucleotides which remain attached to the substrate.

In contradistinction, the instant claims specifically recite contacting an in situ produced nucleic acid array that includes at least one depurination probe feature having a depurination probe with a sample including a target nucleic acid that specifically binds to the depurination probe and detecting the amount of resultant binding complexes of the depurination probe and the target nucleic acid in the depurination probe feature to determine the presence of depurination reaction products on the surface.

At no point in the process of McGall is the substrate contacted with a sample comprising a target nucleic acid; the objects of analysis of McGall are entirely synthesized *in situ* on the substrate prior to the assay. Hence, there is no binding of a target nucleic acid to any of the probes, there is no detecting of a binding complex and there is no detection of the presence of resultant binding complexes on the surface taught by McGall. Rather, the synthesized probes are merely labeled and subjected to a test condition, wherein one or more of the labeled probes may be

cleaved from the array due to a depurination event. The sole detection step is the detection of probes remaining on the substrate subsequent to exposure to the test condition.

The Examiner cites column 13, lines 33-52 of McGall multiple times as allegedly teaching treatment of an array with a sample suspected of containing an analyte under conditions sufficient for binding, detecting the presence of nucleic acid analytes in the sample, and that the sample includes a collection of labeled target nucleic acids that specifically bind to the nucleic acid depurination features (Final Rejection, page 3).

The Appellants submit that this cited passage, also, is incorrectly interpreted by the Examiner. In addition to the Section V "Rates of Depurination" technique from which the other passages cited by the Examiner are taken (column 9, line 22), the disclosure of McGall teaches several other techniques (please consult McGall, column 6, line 12; column 6, line 27; column 8, line 50; column 10, line 35).

Following the description of the different techniques, McGall then provides a general discussion of signal detection and interpretation (please consult McGall, column 11, line 52), in which is discussed a laundry list of issues relating to the use of arrays with CCD image detection devices, computers and data analysis. It is this section of the disclosure which the Examiner cites as describing the claimed elements.

However, as is plain to one of skill in the art, McGall establishes no relationship between the "target nucleic acids" of column 13 and any molecules mentioned in the "Rates of Depurination" technique which would communicate the presence of the claimed elements. Specifically, by way of example, McGall nowhere teaches "hybridization" of the *in situ*-synthesized probes to "target nucleic acids" which would have an "on- or off-rate," and nowhere teaches that the labeled *in situ*-synthesized probes, once cleaved from the substrate by a test condition, would or could reanneal at any rate such that an "equilibrium" could be measured. The

citation is made out of context and, as such, constitutes quintessential cherry picking of phrases from a reference in order to cobble together the Appellants' invention.

Accordingly, the cited passages and figure provide no description of the claimed elements and, indeed, make clear the distinctions between McGall and the claimed method, as discussed above. McGall therefore fails to teach multiple elements of the claims.

Since Weng was cited solely for the hybridization element, it fails to remedy the several deficiencies of McGall. The rejection may be reversed for this reason alone.

Moreover, an element of Claim 1 is detecting the amount of resultant binding complexes of the depurination probe and target nucleic acid in the depurination probe feature to determine the presence of depurination reaction products on the surface.

The Examiner acknowledges that McGall is deficient in that it fails to teach or suggest the use of a hybridization condition as a test condition for determining depurination. The Examiner, therefore, relies upon Weng to remedy the deficiencies of McGall. The Examiner asserts that it would have been obvious to modify the depurination test conditions as taught by McGall with the hybridization conditions disclosed in Weng.

The Appellants, however, respectfully disagree and contend that a *prima facie* case of obviousness has not been established because the recited combination still fails to teach or suggest all the elements of the rejected claims.

As set forth above, an element of Claim 1 is detecting the amount of resultant binding complexes of depurination probes and target nucleic acids in the depurination probe feature to determine the presence of depurination reaction products on the surface. Even were one to combine the references in the manner

suggested, the resultant method would still be deficient in that it would fail to teach or suggest this element of the rejected claims.

Specifically, the Appellants contend that even were McGall to be modified so as to employ hybridization as a test condition, the proposed combination would not result in detecting the amount of binding complexes of depurination probes and target nucleic acids in the depurination probe feature. The modification of McGall would not result in this element being present because McGall is not concerned with determining binding complexes, but rather to determining a depurination event. Hence, McGall discloses that subsequent to subjecting the substrate to a test condition, the substrate is exposed to cleavage conditions that result in depurinated oligonucleotides being cleaved from the substrate (see column 9, lines 50-53). The remaining probes (e.g., the probes which have not been depurinated) are then detected and the amount of depurination is determined by the reduction in the surface tag in the region subjected to the test condition (see column 9, lines 62-63).

As such, even were McGall to be modified in view of Weng, at no point would the modified combination teach or suggest detecting an amount of binding complexes of depurination probes and target nucleic acids in a depurination probe feature on the surface.

Rather, even if modified McGall would still be directed to detecting the amount of non-depurinated probes that have not been cleaved from the surface of the substrate, which by definition, are not depurination reaction products, as is claimed. Hence, the use of hybridization as a test condition, disclosed by Weng, does nothing to remedy this deficiency.

In maintaining the rejection, the Examiner asserts in the Advisory Action of March 7, 2007 that McGall in view of Weng teaches that all of the depurination probes, including those "that were in complexes" but are no longer on the surface, are detected by way of the absence of signal in the treated area.

However, the Appellants firstly note that, as discussed above, the "probe" of McGall has no "target". As such, there are no features comprising depurination probes which are contacted with a sample containing a target, as is claimed.

Further, "detection of depurination products" does not exhaust the limitations of the instant claims, which specifically recite detecting the amount of resultant binding complexes of the depurination probe and the target nucleic acid in the depurination probe feature to determine the presence of depurination reaction products on the surface.

The detection of cleaved products which are no longer found on the features or surface described by McGall, regardless of the method of detection, expressly fails to meet these limitations.

In view of the above, the Appellants contend that a *prima facie* case of obviousness has not been established because the recited combination of references fails to teach or suggest all the elements of the rejected claims, namely contacting an in situ produced nucleic acid array that includes at least one depurination probe feature having a depurination probe with a sample including a target nucleic acid that specifically binds to the depurination probe and detecting the amount of resultant binding complexes of the depurination probe and the target nucleic acid in the depurination probe feature to determine the presence of depurination reaction products on the surface.

Group II: Claim 8

As noted above, independent claim 1 is drawn to a method of detecting the presence of depurination reaction products on a surface of an in situ produced nucleic acid array, the method including contacting an in situ produced nucleic acid array that includes at least one depurination probe feature having a depurination probe with a sample including a target nucleic acid that specifically binds to the depurination probe and detecting the amount of resultant binding complexes of the depurination probe and the target nucleic acid in the depurination probe feature to

determine the presence of depurination reaction products on the surface.

Claim 8 is drawn to the method according to Claim 7, in which the array includes at least one early depurination probe feature and at least one late depurination probe feature.

The Examiner asserts that McGall et al. teaches all elements of the independent claim except hybridization of nucleic acids as a test condition. To remedy this deficiency, the Examiner cites Weng which assertedly teaches hybridizing target nucleic acids in the form of mRNA to a microarray as a test condition.

Without repeating the entirety of the argument, the Appellants submit that, for the reasons detailed above, since McGall describes assaying depurination by synthesizing oligonucleotides on a substrate *in situ*, labeling them, exposing them to a potentially depurinating condition, and detecting labeled, non-depurinated oligonucleotides remaining on the substrate using a protocol in which a "probe" is without a target, McGall fails to teach, either expressly or inherently, contacting an in situ produced nucleic acid array that includes at least one depurination probe feature having a depurination probe with a sample including a target nucleic acid that specifically binds to the depurination probe and detecting the amount of resultant binding complexes of the depurination probe and the target nucleic acid in the depurination probe feature to determine the presence of depurination reaction products on the surface, as is claimed.

With regard to the claim of this group, the Appellants submit that the combined references additionally fail to teach an array including at least one early depurination probe feature and at least one late depurination probe feature.

In the Final Office Action of December 22, 2006, the Examiner asserts that McGall also teaches early and late depurination probe features; namely, the depurination features occur at positions in the sequence relative to the surface

(Figures 8 and 9).

However, the Appellants firstly note that, as discussed above, the "probe" of McGall has no target. As such, there are no features comprising depurination probes which are contacted with a sample containing a target, as is claimed.

Moreover, upon reading the instant application, one of skill in the art readily understands that the claim as written refers to, for example, "early" or "late" probes whose synthesis is started at different increments of the *in situ* synthesis protocol (see, for example, the specification at page 17, line 7 through page 18, line 15), not merely that different features are synthesized identically one after the other, as interpreted by the Examiner.

As such, the ordinarily skilled artisan readily understands that the claim in light of the specification identifies early and late probes which are distinguished by the cycle of the full-length synthesis during which their own synthesis commences. McGall is completely silent with regard to differentiating probes in this or any similar manner, and thus additionally fails to teach the limitations of this claim.

Group III: Claim 9

As noted above, independent claim 1 is drawn to a method of detecting the presence of depurination reaction products on a surface of an in situ produced nucleic acid array, the method including contacting an in situ produced nucleic acid array that includes at least one depurination probe feature having a depurination probe with a sample including a target nucleic acid that specifically binds to the depurination probe and detecting the amount of resultant binding complexes of the depurination probe and the target nucleic acid in the depurination probe feature to determine the presence of depurination reaction products on the surface.

Claim 9 is drawn to the method according to Claim 1, in which the array includes two or more identical depurination probe features whose synthesis was

started at different times.

The Examiner asserts that McGall et al. teaches all elements of the independent claim except hybridization of nucleic acids as a test condition. To remedy this deficiency, the Examiner cites Weng which assertedly teaches hybridizing target nucleic acids in the form of mRNA to a microarray as a test condition.

Without repeating the entirety of the argument, the Appellants submit that, for the reasons detailed above, since McGall describes assaying depurination by synthesizing oligonucleotides on a substrate *in situ*, labeling them, exposing them to a potentially depurinating condition, and detecting labeled, non-depurinated oligonucleotides remaining on the substrate using a protocol in which a "probe" is without a target, McGall fails to teach, either expressly or inherently, contacting an in situ produced nucleic acid array that includes at least one depurination probe feature having a depurination probe with a sample including a target nucleic acid that specifically binds to the depurination probe and detecting the amount of resultant binding complexes of the depurination probe and the target nucleic acid in the depurination probe feature to determine the presence of depurination reaction products on the surface, as is claimed.

With regard to the claim of this group, the Appellants submit that the combined references additionally fail to teach an array including two or more identical depurination probe features whose synthesis was started at different times.

In the Final Office Action of December 22, 2006, the Examiner asserts that McGall also teaches arrays including two or more features whose synthesis was started at different times; namely, areas on the surface are sequentially synthesized (column 9, lines 30-35).

However, the Appellants firstly note that, as discussed above, the "probe" and "target" of McGall are the same molecule. As such, there are no features comprising

depurination probes which are contacted with a sample containing a target, as is claimed.

Moreover, upon reading the instant application, one of skill in the art readily understands that the claim as written refers to, for example, "early" or "late" probes, or "staggered start" probes, i.e. probes all of which have the same sequence and length, but whose synthesis is started at different increments of the *in situ* synthesis protocol (see, for example, the specification at page 17, line 7 through page 18, line 15), not merely that different features are synthesized identically one after the other, as interpreted by the Examiner.

As such, the ordinarily skilled artisan readily understands that the claim in light of the specification identifies probes which are distinguished by the cycle of the full-length synthesis during which their own synthesis commences. McGall is completely silent with regard to differentiating probes in this or any similar manner, and thus additionally fails to teach the limitations of this claim.

Accordingly, for at least these reasons the cited art fails to teach or suggest an array including two or more identical depurination probe features whose synthesis was started at different times, as is claimed.

Group IV: Claim 13

As noted above, independent claim 1 is drawn to a method of detecting the presence of depurination reaction products on a surface of an in situ produced nucleic acid array, the method including contacting an in situ produced nucleic acid array that includes at least one depurination probe feature having a depurination probe with a sample including a target nucleic acid that specifically binds to the depurination probe and detecting the amount of resultant binding complexes of the depurination probe and the target nucleic acid in the depurination probe feature to determine the presence of depurination reaction products on the surface.

For reference, Claim 12 claims the method according to Claim 11, in which the method is a method of evaluating the quality of an in situ nucleic acid array synthesis fabrication protocol Claim 11 claims the method according to Claim 1, in which the method further includes evaluating the level of depurination that occurred during in situ fabrication of the array.

The claim of this group, Claim 13, is drawn to the method according to Claim 12, in which the method is employed to evaluate the quality of a plurality of nucleic acid arrays fabricated according to the protocol.

The Examiner asserts that McGall et al. teaches all elements of the independent claim except hybridization of nucleic acids as a test condition. To remedy this deficiency, the Examiner cites Weng which assertedly teaches hybridizing target nucleic acids in the form of mRNA to a microarray as a test condition.

Without repeating the entirety of the argument, the Appellants submit that, for the reasons detailed above, since McGall describes assaying depurination by synthesizing oligonucleotides on a substrate *in situ*, labeling them, exposing them to a potentially depurinating condition, and detecting labeled, non-depurinated oligonucleotides remaining on the substrate using a protocol in which a "probe" is without a target, McGall fails to teach, either expressly or inherently, contacting an in situ produced nucleic acid array that includes at least one depurination probe feature having a depurination probe with a sample including a target nucleic acid that specifically binds to the depurination probe and detecting the amount of resultant binding complexes of the depurination probe and the target nucleic acid in the depurination probe feature to determine the presence of depurination reaction products on the surface, as is claimed.

With regard to the claim of this group, the Appellants submit that the combined references additionally fail to teach the method according to Claim 12, in which the method is employed to evaluate the quality of a plurality of nucleic acid

arrays fabricated according to the protocol.

In the Final Office Action of December 22, 2006, the Examiner asserts that McGall also teaches the method is employed to evaluate the quality of a plurality of nucleic acid arrays fabricated according to said protocol; namely, arrays in different test areas on the substrate are independently evaluated (column 9, lines 38-49).

However, the Appellants note that the cited passage refers to different features, "R_1" and "R_2", on a single substrate (see also Figure 8, plainly illustrating that the areas are two features on a single substrate; i.e., a single "array").

Accordingly, for at least this reason the cited art fails to teach or suggest that the method is employed to evaluate the quality of a plurality of nucleic acid arrays fabricated according to the protocol, as is claimed.

In view of the arguments above, the Appellants submit that the combined teachings of McGall and Weng et al. fail to make obvious the claims of Groups I-IV and respectfully request reversal of this rejection.

SUMMARY

I. Claims 21-25 are not anticipated under 35 U.S.C. § 102(b) by McGall (US Patent No. 5,843,655) because McGall fails to teach or suggest , either expressly or inherently, contacting a nucleic acid array including features each having a depurination probe and a nucleic acid ligand that specifically binds to the nucleic acid analyte with a sample suspected of including the analyte under conditions sufficient for binding of the analyte to the nucleic acid ligand on the array to occur; and detecting the presence of binding complexes of the nucleic acid ligand and the analyte on the surface of the array.

II. Claims 1-13 are not obvious under 35 U.S.C. § 103(a) over McGall (US Patent No. 5,843,655) in view of Weng et al. (US Patent No. 6,691,042) because Weng et al. fails to remedy the fundamental deficiencies in the teachings of McGall,

namely, that McGall fails to teach target nucleic acids, binding of the target nucleic acids to depurination probes on a feature or surface, and detection of depurination products on the feature or surface.

RELIEF REQUESTED

The Appellants respectfully request that the rejection of Claims 21-25 under 35 U.S.C. § 102 and the rejection of Claims 1-13 under 35 U.S.C. § 103 be reversed, and that the application be remanded to the Examiner with instructions to issue a Notice of Allowance.

Respectfully submitted,

Date: June 15, 2007

By: _____
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CLAIMS APPENDIX

1. A method of detecting the presence of depurination reaction products on a surface of an in situ produced nucleic acid array, said method comprising:

(a) contacting an in situ produced nucleic acid array that includes at least one depurination probe feature having a depurination probe with a sample comprising a target nucleic acid that specifically binds to said depurination probe; and

(b) detecting the amount of resultant binding complexes of said depurination probe and said target nucleic acid in said depurination probe feature to determine the presence of depurination reaction products on said surface.

2. The method according to Claim 1, wherein said method is a method of determining the amount of depurination reaction products on said surface.

3. The method according to Claim 2, wherein said amount is a relative amount.

4. The method according to Claim 1, wherein said target nucleic acid is labeled and said detecting comprising detecting a signal from said depurination probe feature.

5. The method according to Claim 4, wherein said label is fluorescent and said signal is a fluorescent signal.

6. The method according to Claim 5, wherein said fluorescent signal has an intensity that is inversely proportional to the amount of depurination reaction products in said depurination probe feature.

7. The method according to Claim 1, wherein said array includes two or more different depurination probe features each corresponding to a distinct depurination probe.

8. The method according to Claim 7, wherein said array includes at least one early depurination probe feature and at least one late depurination probe feature.

9. The method according to Claim 1, wherein said array includes two or more identical depurination probe features whose synthesis was started at different times.

10. The method according to Claim 1, wherein said depurination probe has a known deblock dose.

11. The method according to Claim 1, wherein said method further comprises evaluating the level of depurination that occurred during in situ fabrication of said array.

12. The method according to Claim 11, wherein said method is a method of evaluating the quality of an in situ nucleic acid array synthesis fabrication protocol.

13. The method according to Claim 12, wherein said method is employed to evaluate the quality of a plurality of nucleic acid arrays fabricated according to said protocol.

21. A method of detecting the presence of a nucleic acid analyte in a sample, said method comprising:

(a) contacting a nucleic acid array comprising a set of two or more nucleic acid depurination features each having a depurination probe and a nucleic acid ligand that specifically binds to said nucleic acid analyte with a sample suspected of comprising said analyte under conditions sufficient for binding of said analyte to said nucleic acid ligand on said array to occur; and

(b) detecting the presence of binding complexes of said nucleic acid ligand and said analyte on the surface of said array to detect the presence of said nucleic acid analyte in said sample.

22. The method according to Claim 21, wherein said sample comprises a collection of labeled target nucleic acids that specifically bind to said nucleic acid depurination features.

23. A method comprising transmitting a result from a reading of an array according to the method of Claim 21 from a first location to a second location.

24. The method according to Claim 23, wherein said second location is a remote location.

25. A method comprising receiving a transmitted result of a reading of an array obtained according to the method Claim 21.

EVIDENCE APPENDIX

No evidence that qualifies under this heading has been submitted during the prosecution of this application, and as such it is left blank.

RELATED PROCEEDINGS APPENDIX

As stated in the *Related Appeals and Interferences* section above, there are no other appeals or interferences known to Appellants, the undersigned Appellants' representative, or the assignee to whom the inventors assigned their rights in the instant case, which would directly affect or be directly affected by, or have a bearing on the Board's decision in the instant appeal. As such this section is left blank.